II. RESPONSE TO OFFICIAL ACTION OF OCTOBER 21, 2004

A. Status of the Claims

Claims 26 and 34-62 were pending in the case at the time of the Official Action, dated October 21, 2004. All claims stand rejected. Claims 26, 34, and 38-62 stand rejected under 35 U.S.C. § 112, first paragraph. Claims 26, 34, and 38-62 were also rejected for obviousness-type double patenting over claims 1-21 of U.S. Patent No. 6,033,682, claims 1-57 of U.S. Patent No. 6,348,208, claims 1-33 of U.S. Patent No. 6,419,948, claims 1-30 of U.S. Patent No. 6,562,365, claims 1-36 of U.S. Patent No. 6,699,495, and claims 1-26 of U.S. Patent No. 6,528,082. Finally, claims 26 and 34-62 were rejected under 35 U.S.C. § 103 as obvious. Although the Action states that claims 35 and 36 also stand rejected, no basis was presented for rejecting these claims.

B. Rejections Based on 35 U.S.C. § 112, First Paragraph, are Overcome

Claims 26, 34, and 38-62 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The Action argues that the "claims are broad as they encompass a number of 'conditions' that are stimulated or caused by immune dysfunction or immune deficiency."

Applicant respectfully asserts that the claims are enabled because it is well within the skill of one in the art to determine whether a condition produced by immune system dysfunction is associated with reduced levels of γ-interferon production, and whether administering the R(-) enantiomer of desmethylselegiline or a pharmaceutically acceptable acid addition salt thereof leads to an increase in γ-interferon production. The underlying complexity of the immune system does not mean that the pending claims are not enabled. Measuring reduced levels or increased levels of

γ-interferon in a mammal are well within the skill of one in the art, and do not require undue experimentation.

The Action begins by stating that the "nature of the invention is extremely complex in that it encompasses anticipating multiple complex diseases or disorders and subsequently administering the instant composition." Whether or not the claims will encompass multiple complex diseases or disorders is irrelevant to the question of enablement, since one of skill in the art will clearly be able to identify conditions produced by immune system dysfunction associated with reduced levels of γ-interferon production. Similarly, the Action's statement that "the described or claimed conditions may or may not be caused by gamma-interferon reduction leading to immune dysfunction" is inappropriate for arguing that the claims are not enabled. The question is whether one of skill in the art can identify conditions that fall within the genus of conditions produced by immune system dysfunction is associated with reduced levels of γ-interferon production without undue experimentation. The answer to this question is yes.

Reduced levels of γ-interferon production, and the role it plays in immune system dysfunction, is clearly understood in the art. The reference attached hereto as Exhibit A, Billiau, A., *Interferon-γ: Biology and Role in Pathogenesis*, ADV. IMMUNOL. 62:61-130 (1996), clarifies the correlation of IFN-γ to conditions related to immune deficiency such as cancer and AIDS, as well as autoimmune diseases. The cytokine IFN-γ plays a central role in the immune system, and immune dysfunction related to IFN-γ has been recognized in both immune deficiency and autoimmune diseases:

> Medical interest in IFN-γ stems from awareness that a prominent target cell of IFN-γ, the macrophage, occupies a central position in the immune system. Adequate function of the IFN-γ/macrophage system is essential for natural as well as acquired resistance to infection and cancer. Malfunctioning of the system is recognized to be instrumental in inflammatory and autoimmune disease. *Id.* at 62.

Thus, although immune system function "is a complex interplay of several interleukins or chemokines," IFN-γ has a central position in the immune system and is involved in both immune deficiency and autoimmune diseases.

The Action next argues that the "specification fails to provide any guidance or rationale showing that the claimed method is effective to completely treating [sic] any or all disorders produced by immune dysfunction, associated with reduced levels of gamma-IFN or to extrapolate the data provided to al [sic] immune dysfunction conditions, that are known to-date or yet to be discovered."

Applicants submit that this is an improper rejection. The claims are drawn to "treating a condition" and the Examiner has inserted the limitation that the method must "completely treat any and all disorders..." The methods of the claims are not described as total cures to any disease or condition, but rather as methods of treating. This subject matter is analogous to that in *In re Sichert*, 566 F.2d 1154, 1160, 196 USOQ 209, 212 (CCPA 1977), in which the appeal court used the analogy of over the counter ointment drugs which have the purpose of stimulating blood circulation. Use of an ointment to stimulate circulation and alleviate pain is not the same as treatment directed at curing the disease (arthritis) that has caused the condition. Furthermore, Applicants are not required to demonstrate "full treatment" of a disease prior to filing an application. This issue is addressed by the Federal Circuit:

> Testing for the full safety and effectiveness of a prosthetic device is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings. *Scott v. Finney* 32 USPQ2d 1115, 1120

Therefore, there is no requirement for patentability that the claimed methods be effective to treat any or all conditions produced by immune system dysfunction associated with reduced levels of

γ-interferon production. "The presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art." MPEP § 2164.08(b). The pending claims clearly claim subject matter that a skill person could determine would be inoperative or operative without undue experimentation, because on of skill in the art can clearly determine whether the administration of R(-)-desmethylselegiline results in increased γ-interferon production.

As stated in the specification, the ability of R(-)-desmethylselegiline to restore γ-interferon production supports the conclusion that this enantiomer of desmethylselegiline is able to treat a condition in a mammal produced by immune system dysfunction. See specification, Example 11, beginning on p. 38. Given that the malfunctioning of the IFN-γ/macrophage system is recognized to be instrumental in inflammatory and autoimmune diseases, the ability of R(-)-desmethylselegiline to restore IFN-γ production will "bolster a patient's normal immunological defenses [and] be beneficial in the treatment of a wide variety of acute and chronic diseases including cancer, AIDS, and both bacterial and viral infections." See specification, p. 38, lines 12-14.

Further, the specification provides sufficient guidance to one of skill in the art for administering the instant composition to mammals for treating any or all of the disorders claimed. See specification, p. 9, line 8 to p. 10, line 20. For example, on p. 9, lines 8-21, the specification states:

> The optimal daily dose of R(-)DMS, S(+)DMS, or of a combination, such as a racemic mixture, of R(-)DMS and S(+)DMS, useful for the purposes of the present invention is determined by methods known in the art, *e.g.*, based on the severity of the disease or condition being treated, the condition of the subject to whom treatment is being given, the desired degree of therapeutic response, and the concomitant therapies being administered to the patient or animal. Ordinarily, however, the attending physician or veterinarian will administer an initial dose of at least about

> 0.015 mg/kg, calculated on the basis of the free secondary amine, with progressively higher doses being employed depending upon the route of administration and the subsequent response to the therapy... These guidelines further require that the actual dose be carefully titrated by the attending physician or veterinarian depending on the age, weight, clinical condition, and observed response of the individual patient or animal.

A person skilled in the art could readily determine the effective amount of R(-)--desmethylselegiline required to achieve a therapeutic effect based upon animal pharmacology and early phase clinical trials in humans, both of which are standard activities and practices in the pharmaceutical industry.

Finally, the Action states that "the practitioner would turn to trial and error experimentation in order to determine the 'conditions' caused by immune system dysfunction [sic] (associated with gamma-IFN) in mammals that would respond to the claimed method of treatment (employing the claimed composition)." But as clearly set forth above, the immune system dysfunction conditions associated with associated with reduced levels of γ-interferon production are already well known to those of skill in the art, and any such conditions that did not respond to the claimed method of treatment by demonstrating an increase in γ-interferon production in the mammal, which could easily be identified by one of skill in the art, would not fall within the scope of the claim.

Based on the foregoing arguments, Applicant respectfully asserts that the 35 U.S.C. § 112, first paragraph rejection is overcome, and accordingly requests that the Examiner withdraw this rejection.

C. Rejections Based on Double Patenting are Overcome

1. U.S. Patent Nos. 6,348,208, 6,419,948, 6,562,365, and 6,699,495

Claims 26, 34, and 38-62 stand rejected for obviousness-type double patenting. The Action cites claims 1-57 of U.S. Patent No. 6,348,208, claims 1-33 of U.S. Patent No. 6,419,948, claims

1-30 of U.S. Patent No. 6,562,365, or claims 1-36 of U.S. Patent No. 6,699,495 as the bases for the double patenting rejection. Applicant has attached hereto a terminal disclaimer that overcomes the rejection over claims 1-57 of U.S. Patent No. 6,348,208, claims 1-33 of U.S. Patent No. 6,419,948, claims 1-30 of U.S. Patent No. 6,562,365, and claims 1-36 of U.S. Patent No. 6,699,495. Somerset Pharmaceuticals, Inc. owns U.S. Patent Nos. 6,348,208, 6,419,948, 6,562,365, and 6,699,495. Accordingly, Applicant respectfully requests withdrawal of this rejection for obviousness-type double patenting.

2. U.S. Patent No. 6,033,682

Claims 26, 34, and 38-62 stand rejected for obviousness-type double patenting. The Action cites claims 1-21 of U.S. Patent No. 6,033,682 as the basis for the double patenting rejection.

> Obviousness-type double patenting requires rejection of an application claims when the claimed subject matter is not patentably distinct from the subject matter claimed in a commonly owned patent when the issuance of a second patent would provide unjustified extension of the term of the right to exclude granted by a patent. MPEP § 804.II.B.1.

Applicant asserts that the presently pending claims, which are all directed to R(-)-desmethylselegiline, are *patentably distinct* from the claims of U.S. Patent No. 6,033,682, which are all directed to S(+)-desmethylselegiline, and that the issuance of the present application will not provide an unjustified extension of the term of the right to exclude granted by a patent. The specification clearly teaches that R(-)-desmethylselegiline and S(+)-desmethylselegiline are the two enantiomers of desmethylselegiline, and have surprisingly different therapeutic activities, and therefore applications. In addition, the data presented in the present application clearly demonstrates the different therapeutic activities of the two enantiomers, and that they are patentably distinct. Therefore, Applicant respectfully request reconsideration and withdrawal of this rejection for obviousness-type double patenting.

3. U.S. Patent No. 6,528,082

Claims 26, 34, and 38-62 stand rejected for obviousness-type double patenting. The Action cites claims 1-26 of U.S. Patent No. 6,033,682 as the basis for the double patenting rejection. Applicant respectfully asserts that the claims of the '682 patent, which are directed to obtaining a selegiline therapeutic effect in a patient with a neoplastic disease or condition, are *patentably distinct* from the claims of the presently pending application. The disclosure of the R(-)-desmethylselgiline to treat neoplastic diseases or conditions does not render obvious methods of administering this enantiomer to treat conditions in mammals produced by immune system dysfunction that are associated with reduced levels of γ-interferon production. These method claims are directed to two distinct categories of conditions, and the claims of the '682 patent are not directed to the mechanism by which R(-)-desmethylselgiline is able to treat neoplastic diseases or conditions. Therefore, Applicant respectfully request reconsideration and withdrawal of this rejection for obviousness-type double patenting.

D. Rejections Based on Obviousness are Overcome

The Action rejects claims 26, 34, and 38-62 as being obvious over Borbe in view of Barton et al. and Balsa et al. The Action states that (1) Borbe teaches the oral administration of DMS to rats, which is an MAO-B inhibitor; (2) Barton associates immune dysfunction with conditions such as AIDS, Kaposi's sarcoma etc.; and (3) Balsa teaches that the activity of MAO-B is predominant in lymphocytes (L) and granulocytes (G). The Action concludes that "[o]ne of an ordinary skill in the art would have expected DMS, a monoamine oxidase inhibitor, to be effective in treating AIDS, tumors, cancers and other immune deficient conditions by inhibiting the action of MAO-B of immune cells i.e., lymphocytes and granulocytes."

Applicant respectfully traverses this rejection because the Action fails to establish a *prima facie* case of obviousness. MPEP § 2143 sets forth that to establish a *prima facie* case of obviousness, there must be some suggestion or motivation to combine reference teachings, there must be a reasonable expectation of success, and the references when combined must teach or suggest all of the claim limitations.

First, the three references offer no teaching, suggestion, or motivation to combine their teachings to produce the claimed invention. Second, even if the references are combined (without any teaching, suggestion, or motivation), the references do not teach or suggest all elements of the pending claims. As the Action admits, the references do not explicitly state a reduction in the levels of γ-interferon, which is an element of each of the pending claims. Instead, the Action argues that "absent showing the evidence to the contrary, it is the position of the examiner that the claimed composition implicitly restores the levels of gamma-IFN." But the pending claims are not directed to a composition, they are directed to methods of administering R(-)-desmethylselegiline to treat a condition in a mammal produced by immune system dysfunction that is associated with reduced levels of γ-interferon production. The examiner has presented no evidence that any of the references, alone or in combination, disclose every element of the claimed methods. Since there is no motivation or suggestion to combine the references, and even if combined the references do not disclose every element of the pending claims, there can be no expectation of success. Therefore, the Action has not met its burden to establish a *prima facie* case of obviousness. Accordingly, Applicant respectfully asserts that the 35 U.S.C. § 103(a) rejection is overcome, and requests that this rejection be withdrawn.

III. CONCLUSION

In light of the foregoing amendments and remarks, Applicants respectfully submit that all claims are in condition for allowance, and solicit an early indication to that effect. Should Examiner Channavajjala have any questions regarding this response, please contact attorney of record, Margaret Sampson at (512) 542-8569.

Please date stamp and return the enclosed postcard evidencing receipt of these materials.

Respectfully submitted,

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